

AMENDMENT TO THE SPECIFICATION

Please delete the “Technical Field” Section on Page 1, lines 7-10 of the specification and replace it with the following section.

Field of the Invention

The present invention generally relates to a method for treating oncological diseases by administering an agent that destroys extracellular DNA in the blood of a cancer patient.

Please delete the “Background Art” Section on Page 1, line 12 to Page 4, line 16 of the specification and replace it with the following section.

Background of the Invention

Populations of tumor cells developing in patients have a very high genetic variability which exceeds a same for healthy cells. Genetic variability of cancer cell populations causes mutated cells to generate phenotypes that (1) are insensitive to immune and morphogenetic control, (2) have an ability to invade and metastasize, and (3) are desensitized to cancer therapies. Selection and clonal expansion of cancer cells are both considered to underlie a biological and a clinical progression of tumors. For this reason, an approach of modern cancer therapies is based on a destruction of cancer cell clones in patients by means of chemotherapy, immunotherapy, biotherapy, surgical methods, or a combination thereof.

Chemotherapy, radiotherapy, biotherapy and more recent immunotherapy are the most commonly used non-surgical methods of treating cancer diseases. These therapies are administered to destruct, to damage or to inactivate a cancer cell's intracellular DNA.

The chemotherapy approach is based an administration of well known compounds:

platinum preparations, anthracycline antibiotics, alkylating agents and podophyllotoxins. The radioimmunotherapy approach is based on irradiation of intracellular DNA of cancer cells' nuclei. Alpha particles from alpha emitters are specially delivered into the cancerous cells to increase effects on those cells' intracellular DNA. Biotherapeutic and immunotherapeutic approaches are based on an induction of apoptosis of cancer cells, which induces death of the cancer cell. Apoptosis starts with an activation of intracellular nucleuses and follows with a degradation of the tumor cell's intracellular DNA. This process is accomplished, for example, by means of administering genotherapeutic constructions that consist of genes that induce apoptosis or genes coding the factors which activate the nucleuses.

Aguilera, *et al.* discloses in U.S. Patent No. 6,455,250 endonuclease Endo SR to treat cancer diseases by mode of its intracellular delivery into target cells. This method and chemotherapy, with Etopozide-4-Demetilpodophylotoxe (4,6-O-R)-etiliden-b-D-glycopiranozid, were both selected for a prototype of the present invention.

Topoizomerase II is an essential cell enzyme that regulates many aspects of DNA function. The enzyme is responsible for interconversion of different topological forms of intracellular DNA by means of a generation of transitory breaks of double-stranded DNA. Etopozide, as a Topoizomerase II inhibitor, increases an intracellular level of "broken DNA-Topoizomerase II" complexes.

The result of this drug's influence is an accumulation of double-stranded intracellular DNA breaks which lead to the cell's death. A drawback of this method prototype, along with well-known methods, is their low efficacy. These methods imply that mostly the cancer cells' intracellular DNA is the therapeutic target. Because of high genetic variability, these cancer cells

become desensitized to the therapies before they are adequately eliminated. A further disadvantage is that the intracellular DNA is a difficult-to-approach target; it leads to necessary high-dosing antineoplastic chemotherapy and/or other complicated delivery systems. A final disadvantage to these methods is that they are highly toxic: their influence on cancerous cells' intracellular DNA also damages healthy cells' DNA.

Please delete the “Disclosure of the Invention” Section on Page 4, line 18 to Page 7, line 9 of the specification and replace it with the following section.

Summary of the Invention

An object of this invention is to develop a highly efficient cancer therapy having low toxicity. It is an object to resolve the foregoing drawbacks by administering into systemic circulation an agent which destroys blood extracellular DNA.

The agent is introduced in doses that alter an electrophoretic profile of blood extracellular DNA, which could be detectable by pulse-electrophoresis. Doses of the agent are introduced according to a regime schedule that provides for plasma hydrolytic activity exceeding 150 Kuntz units/liter of blood plasma. This level can be supported for more than 12 hours within a 24 hour period. The treatment is carried out continuously for no less than 48 hours. In particular, bovine pancreatic DNase can be introduced parenterally in doses ranging from 50,000 Kunitz per day to 250,000,000 per day. These doses are administered anywhere between five and 360 days. In particular, recombinant human Dnase (dornase - alpha) can be parenterally introduced in doses ranging from 0.15 mg/day to 500 mg/day between a five - 360 day period. The treatment may continue for a life of the patient. Additionally, an agent which bounds extracellular DNA, s.a.,

anti-DNA antibodies, can also be introduced to the systemic circulation. A modifying agent can further be introduced into the circulation, which modifies the chemical structure, the conformation, the degree of polymerization, or the association of proteins, lipids and/or ribonucleic acids of the blood's extracellular DNA. A preferred modifying agent may be a ribonuclease enzyme and, more particularly, *Serratia Mercenses*.

The present invention suggests that cancer can be treated by reducing circulating DNA levels. Circulating DNA levels are higher in the blood of cancer patients than in healthy controls. Stroun discloses in U.S. Patent No. 5,952,170 a method of diagnosing cancers, wherein extracellular DNA in the blood is used for diagnostics and for a prognosis of a clinical course of a malignant disease. Hoon and Gocke disclose in U.S. Patent Nos. 6,465,177 and 6,156,504, respectively, a use of blood's extracellular DNA to define mutations in oncogenes and microsatellite fragments of genes. These patents also disclose usages of blood's extracellular DNA for studying genome instability in tumors.

There is no systematic analysis of blood's extracellular DNA spectrum and its biological role prior to this invention. A search of the prior art reveals no published data concerning a research of blood's extracellular DNA performed without a polymerase chain reaction ("PCR"). Polymerase chain reactions can pervert a pattern of blood's extracellular DNA because of a specificity of primers which are used for amplification. Until recently, a genetic analysis of extracellular blood DNA was mainly carried out by PCR or by blot-hybridization and it was directed to a study of changes in certain fragments of a genome, s.a., e.g., microsatellites and separate genes during a malignant process.

There is thus no available knowledge about a genetic repertoire of blood's extracellular

DNA in cancer patients, about a biological role of that blood's extracellular DNA in oncopatology, and about the potential therapeutic effects of a destruction, an inactivation or a treatment of these diseases.

The blood's extracellular DNA in cancer patients contains a unique quantitative and qualitative repertoire of genes and regulating genetic elements which greatly differ from that of DNA in a healthy human genome. In contrast to intracellular DNA, extracellular DNA in cancer patients mainly contains unique human genes, including genes which are involved in a development of and a maintenance of malignant behavior in cancer cells. Because blood's extracellular DNA contributes to malignant growth in cancer patients, a destruction of, a modification of, or a binding of blood's extracellular DNA is useful because it slows down that growth. These interventions are very useful in independent therapy and they also increase an effectiveness of traditional methods of treatment.

The aforesaid new characteristics of this invention are based on new ideas about mechanisms of oncological diseases.